MCNEIL LABORATORIES, INC. BIOLOGICAL RESEARCH DEPARTMENT, FORT WASHINGTON, PENNSYLVANIA, U.S.A.

THE CARDIOVASCULAR EFFECTS OF AMINOREX, A NEW ANOREXIGENIC AGENT

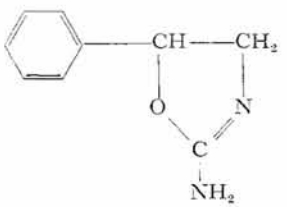
BY

J. YELNOSKY, R. J. HEWSON, J. MUNDY AND J. MITCHELL

(Received for publication 18-1-1966*)*.

ROSZKOWSKI and KELLY (1) have observed the anorexigenic potential of Aminorex (McN-742, FIG. 1) in the rat. Clinical studies have indicated the compound was an effective anorexigenic agent in man (2). This report describes some of the cardiovascular actions of Aminorex and its interactions with certain drugs included to facilitate the pharmacologic classification of this compound.

Aminorex



2-amino-5-phenyl-2-oxazoline

FIG. 1

METHODS AND MATERIALS

Mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg, i.v.) were used. Arterial blood pressure was obtained from a carotid artery connected to a mercury manometer or a Sanborn pressure transducer. A femoral vein was cannulated for i. v. injections.

Direct measurements of the contractile force of the heart were obtained in open-chest

dogs with a strain gauge arch sutured directly to the right ventricle (3). Artificial respiration was carried out with a Palmer pump.

Dogs were presumably depleted of catecholamines after i.p. injections of reserpine (0.5 mg/kg) once a day for 2 consecutive days (4).

Aqueous solutions of the following compounds were used: *l*-epinephrine and *dl*-isopropylnorepinephrine (isoproterenol) as the bitartrates, atropine sulfate, hexamethonium chloride, DMPP (1, 1-dimethyl-4-phenyl piperazinium iodide), *d*-amphetamine sulfate, nethalide (α-[(isopropylamino) methyl]-2-naphthalene-methanol hydrochloride), dibenamine (N,N-dibenzyl-3-chloroethyl-amine hydrochloride), tranylcypromine (2-phenylcyclopropylamine hydrochloride). Dibozane (1,4-bis-(1,4, benzodioxan-2-ylmethyl)piperazine) was dissolved in 0.8 % phosphoric acid and reserpine was prepared either in ethanol and glacial acetic acid or in 20 % ascorbic acid. Aminorex was dissolved in 1 equivalent of 1 N HCl and diluted to a 2 % solution with distilled water.

Results and Discussion

Cardiovascular Effects of Aminorex. Sympathomimetic cardiovascular effects were noted after the first injection of Aminorex (0.5 mg/kg). Maximal increases in contractile force (129 to 262 %), heart rate (12 to 42 beats/min), and mean blood pressure (55 to 142 %) occurred within 3 min after the injection; recovery was complete or nearly complete in 13 to 27 min. A second injection was less effective; contractile force and blood pressure were increased only 12 to 18 and 33 to 48 % respectively. The heart rate was unchanged, decreased or slightly increased. Subsequent injections had little or no effect; however, 2 μg/kg of epinephrine caused marked increases in the contractile force and blood pressure.

The intensity of the cardiovascular effects of Aminorex was dose related. An injection of 25 μg/kg produced slight transient increases in the contractile force and blood pressure; a more intense response followed an injection of 125 μg/kg. A direct dose response relationship was also noted in studies in closed-chest dogs in which only the blood pressure was measured. Amphetamine was included for comparative purposes (Table I).

Mechanism of the Cardiac Effects. The effects of the beta adrenergic blocking agent, nethalide (5) on the cardiac stimulant effects of Aminorex was studied in 4 dogs. After nethalide the positive inotropic and chronotropic effects of Aminorex (0.5 mg/kg) were abolished or markedly reduced; the blood pressure effects appeared to be slightly decreased. Specifically 7 to 15 min after an i.v. injection of 5 or 10 mg/kg of nethalide, an injection of Aminorex caused a decrease in contractile force (7 to 20 %) in 3 dogs and a relatively small increase (28 %) in one dog.

TABLE I

Blood Pressure Effects of Aminorex and Amphetamine in Anesthetized Dogs

No. of dogs	Dose Aminorex mg/kg i.v.	Average Max. % Inc. in Mean Art. Blood Pressure	Standard Error of the Mean
6	0.1	18	4
12	0.5	34	6
12	1.0	44	6
	Dose amphetamine mg/kg i.v.		
5	0.1	21	4
12	0.5	50	3
6	1.0	72	6

The heart rate was decreased 18 to 30 beats/min. Arterial blood pressure was increased 39 to 80 %. A marked or complete blockade of the cardiac and blood pressure effects of isoproterenol (1.25 μg/kg) was evidence of beta receptor blockade in these tests. It was concluded that the cardiac effects of Aminorex were due mainly, if not completely, to beta receptor stimulation and that the increase in blood pressure was not completely dependent on the cardiac effects.

Mechanism of the Pressor Effects. The pressor effects of Aminorex (1 mg/kg) obtained in 12 dogs were compared with the pressor effects obtained in 5 dogs pretreated with the alpha adrenergic blocking agent, dibenamine. Dibenamine (20 mg/kg) was injected one and one-half to two hours prior to the injection of Aminorex. In the controls, Aminorex caused a maximum average increase in the mean blood pressure of 44 % ± 6. In the dogs pretreated with dibenamine the pressor effect was completely blocked in one dog and was reduced by about 1/2 in 3 dogs suggesting the effect was due, at least in part, to alpha receptor stimulation. A complicating factor was an apparent inability of dibenamine to block the pressor action of Aminorex in 1 dog. Reversal by dibenamine of the hypertensive effect of epinephrine (2 μg/kg) was indicative of alpha receptor blockade in these tests.

Tachyphylaxis. It was noted in the initial experiment that Aminorex tachyphylaxis developed rapidly and was probably not dependent on decreased responsiveness of the dog to sympathomimetics since epinephrine produced marked cardiovascular stimulant effects after the dog was not responding to Aminorex. The nature of the tachyphylaxis was determined to be amphetamine-like. Five dogs received 3 to 5 doses

of Aminorex ranging from 1.25 to 1 mg/kg over a period of 18 to 54 min; tachyphylaxis was clearly evident. Nine to 17 min after the final injection of Aminorex, 1 mg/kg of amphetamine produced little or no increase in the blood pressure while in 6 control dogs the same dose of amphetamine increased the blood pressure by 51 to 84 %. Cross tachyphylaxis was demonstrated in 3 of the control dogs. These dogs received 2 additional injections of amphetamine over a period of 30 to 47 min which had little or no effect on the blood pressure. Aminorex (0.5 mg/kg) given 6 to 9 min after the final injection of amphetamine was completely or nearly completely inactive; however, 2 μg/kg of epinephrine increased the blood pressure on the average by 45 %.

Cardiovascular Effect of Aminorex in Reserpine-Pretreated Dogs. The sympathomimetic effects of Aminorex appeared to be due mainly to the release of catecholamines. This conclusion was based on results from dogs presumably depleted of catecholamines by pretreatment for 2 days with reserpine. In 3 reserpine-pretreated dogs a dose of 0.5 mg/kg of Aminorex had no effect or increased the contractile force by only 8 and 20 % and the blood pressure by only 7 to 14 % as compared to increases in contractile force and blood pressure in the controls of 129 to 262 % and 55 to 142 % respectively. The heart rate was decreased in 1 dog and increased by 12 to 18 beats/min in 2 dogs, while in the controls the heart rate was increased from 12 to 42 beats/min. The reserpine-pretreated dogs were very responsive to epinephrine; a dose of 2 μg/kg increased contractile force by more than 100 %, blood pressure by 80 to 91 % and heart rate by 30 to 48 beats/min. Additional tests were carried out in 4 close-chest dogs in which only the blood pressure was measured, and the dose of Aminorex was increased to 1 mg/kg. Aminorex was relatively ineffective as a pressor agent in these tests. The maximal increase in mean arterial blood pressure was 69 % less than in the controls; marked pressor responses (60 to 120 mm Hg) followed injections of 1 or 2 μg/kg of epinephrine.

The apparent release of catecholamines by Aminorex does not appear to be dependent on a centrally induced increase in activity of the sympathetic nervous system since the pressor effects of Aminorex were enhanced in 4 dogs pretreated with hexamethonium (2 mg/kg). Fifteen minutes after the injection of hexamethonium an injection of 0.1 mg/kg of Aminorex caused an average maximal increase in the mean blood pressure of 69 % ± 6 compared to 18 % ± 4 in the controls. Potentiation of the pressor effect of Aminorex by hexamethonium was probably due, at least in part, to blockade of the antagonizing action

of the vagus nerve. Complete or partial blockade of the pressor response to DMPP (15–30 μg/kg) indicated ganglionic blockade in these experiments.

Aminorex (0.5 mg/kg) produced its usual pressor response in 3 adrenalectomized dogs and in 4 dogs pretreated with atropine (0.5 mg/kg) indicating the response was not mediated by catecholamines released from the adrenal glands and was not due to an A-343-like stimulation of sympathetic ganglia (6).

Interaction of Aminorex with Reserpine. It was desirable for the purpose of classifying Aminorex to determine whether the compound would interact acutely with reserpine in a manner similar to amphetamine (7).

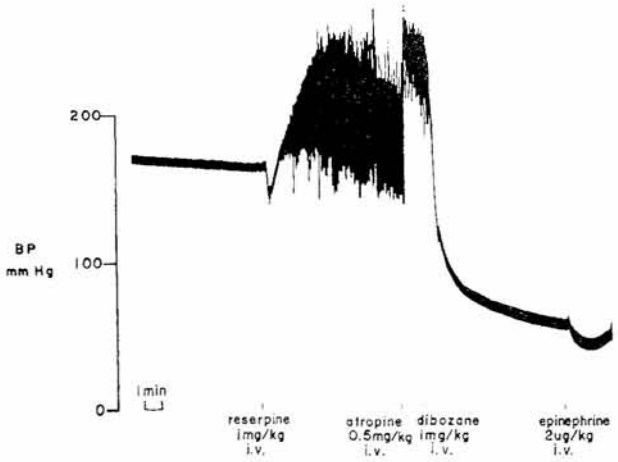


FIG. 2

Pressor effect of reserpine in an anesthetized dog pretreated with Aminorex 30 min before the injection of reserpine.

Enhancement of the pressor effect by atropine and antagonism of the pressor effects of Aminorex and epinephrine by Dibozane, an adrenergic blocking agent, is shown.

Four dogs received 1 mg/kg of reserpine which caused little or no change in the blood pressure. In 30 mins. an injection of 0.1 mg/kg of Aminorex produced a maximum average increase in mean arterial blood pressure 5 times greater than in the controls. Conversely, in 8 dogs, an injection of 1 mg/kg of reserpine 30 min after the injection of 0.5 mg/kg of Aminorex resulted in a marked increase in mean arterial blood pressure (FIG. 2). The pressor effect was enhanced when the antagonistic effect of the vagus nerve was abolished by a bilateral cervical section of the nerve or by an injection of 0.5 mg/kg of atropine.

The reserpine pressor response was immediately reversed by an injection of 0.5 or 1 mg/kg of Dibozane, an alpha receptor adrenergic blocking agent. It was possible that this interaction between reserpine and Aminorex resulted from an increased rate of release of catecholamines. It was noted that reserpine was still capable of producing a marked pressor response after tachyphylaxis developed to Aminorex, suggesting the response after reserpine was not dependent on the release of catecholamines from stores susceptible to the releasing action of Aminorex. These results further point out the similarity of Aminorex to amphetamine (8).

Tranylcypromine. LEE *et al.* (9) have reported that tranylcypromine exerts sympathomimetic effects via a catecholamine release mechanism. This similarity between tranylcypromine, Aminorex and amphetamine led us to include tranylcypromine in this study. Three dogs were given an injection of tranylcypromine (0.1 mg/kg). There was an acute maximal increase in the mean blood pressure of only 6 to 16 %. The same dose of tranylcypromine was given to 4 dogs 5 min after the injection of 1 mg/kg of reserpine. The pressor effect of tranylcypromine was markedly potentiated. Maximal increases in mean blood pressure of 71 to 118 % were obtained within 3 mins. Dibozane (0.2 mg/kg) immediately terminated the response. Reserpine (1 mg/kg) produced marked pressor effects in dogs given 0.5 mg/kg tranylcypromine 30 min beforehand. A marked pressor response following the injection of reserpine also occurred in 2 to 4 dogs when the dose of tranylcypromine was reduced to 0.1 mg/kg and the interval between the injections was reduced to 5 min.

The ability of reserpine to produce hypertension in animals pretreated with tranylcypromine has been previously reported by GARRATTINI *et al.* (10). This effect was considered to be dependent on the monoamine oxidase inhibitory action of tranylcypromine. We believe that the acute amphetamine-like effects of tranylcypromine must also be considered in an analysis of its interaction with reserpine.

SUMMARY

This report describes the cardiovascular effects of Aminorex, a new anorexigenic agent. On the basis of its actions alone and its interactions with reserpine, Aminorex may be classified as an indirect acting sympathomimetic agent.

Some amphetamine-like effects of tranylcypromine are also described.

References

1. — Roszkowski, A. P. and Kelly, N. M. *J. Pharmacol.*, 1963, *140*, 367.
2. — Wood, L. C. and Owen, J. A. *J. new Drugs*, 1965, *5*, 181.
3. — Boniface, K. L., Brodie, O. S. and Walton, R. P. *Proc. Soc. exp. Biol.*, 1953, *84*, 263.
4. — Burn, J. H. and Rand, M. J. *J. Physiol.*, Lond., 1958, *144*, 314.
5. — Black, J. W. and Stephenson, J. S. *Lancet*, 1962, *ii*, 311.
6. — Roszkowski, A. P. *J. Pharmacol.*, 1961, *132*, 156.
7. — Schmitt, H. and Schmitt, H. *Arch. int. Pharmacodyn.*, 1961, *132*, 97.
8. — Yelnosky, J., McGill, J. and Mastrangelo, A. *Arch. int., Pharmacodyn.*, 1966, *159*, 416.
9. — Lee, W. C., Shin, W. H. and Shideman, F. E. *J. Pharmacol.*, 1961, *133*, 180.
10. — Garattini, S., Fresia, P., Mortari, A. and Palma, V. *Med. exp.*, 1960, *2*, 252.